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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SNEDDEN, SHERIDAN	

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,327	TAKAKURA ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003 and 23 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-20,22-24 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *20,30 and 31* is/are allowed.

6)☒ Claim(s) *11-19,22-24,28,29 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. This Office Action is in response to Paper #13, filed 5 May 2003 and Paper #15, filed 23 May 2003. As per paper #13, claims 1-10, 21 and 25-27 have been canceled and Applicant's amendment of claims 11-20 and addition of new claims 28-32 is acknowledged. Additional amendments to claims 11, 13-19 and 30-32 in Paper #15 is acknowledged. Claims 11-20, 22-24 and 28-32 are pending.

Withdrawal of Objections and Rejections

2. The objections and/or rejections not explicitly restated or stated below are withdrawn.

Maintained Objections and Rejections

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 11-18, 22-24 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecule of SEQ ID NO: 1 encoding an antimicrobial protein, does not reasonably provide enablement for a gene sharing 50% sequence identity with SEQ ID NO: 1 encoding an antimicrobial protein. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected,

to make and/or use the invention commensurate in scope with these claims. As currently stated, the invention would include nucleic acid sequences of 50% identity to SEQ ID NO: 1.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention;

In the instant case, the invention is a gene encoding an antimicrobial protein that possesses 50-100 % sequence homology to SEQ ID NOs: 1. The only gene sequence expressly taught is that of SEQ ID NO: 1.

2) the breadth of the claims;

The invention would consist of all genes whose primary sequence shares a 50% to 100% sequence identity to that of SEQ ID NO: 1 and encodes an antimicrobial protein. As stated, the invention is drawn to thousands of gene sequences that would encode thousands of different amino acid sequences.

It cannot be predicted by one of skill in the art that nucleic acids that share at least 50% homology to the gene of SEQ ID NO: 1 will encode a protein with the same antimicrobial activity as the gene of SEQ ID NO: 1. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex

(pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column).

3) the predictability or unpredictability of the art;

The DNA and protein sequence arts are recognized as unpredictable, as minor changes in the nucleotide or amino acid sequences to these molecules may produce profound changes in biological activity. The physiological structure and function of a protein cannot be determined based solely on sequence identity to the primary sequence of the gene of SEQ ID NO: 1.

The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Thus, Lazar *et al.* demonstrated that one or few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

Indeed, a search of the prior art identified a nucleic acid molecule which shares a 53.5% sequence identity with the gene of SEQ ID NO: 1 (see SEQ IN NO: 2 of Kawamura *et al.*). The nucleic acid of Kawamura *et al.* codes for an antitumor protein as opposed to a protein showing antimicrobial activity. Thus, sequence homology does not lead to predictable function.

4) the amount of direction or guidance presented;

The specification discloses a protein that possesses antimicrobial activity, and particularly, possesses antimicrobial activity against *Rhizoctonia solani* and *Pyricularia oryzae*. The specification discloses the cDNA of the above protein.

The claims recite a gene, which contains both introns and exons, which are not adequately disclosed in the specification. No discussion is provided as to the number of introns and exons and to what sequences make up each exon and intron.

Additionally, as the claims recite % homology, the specification fails to indicate what regions or positions of the cDNA or protein are required in order for the protein to maintain antimicrobial activity and thus, leads to greater unpredictability of outcome for predicting function based on % homology.

5) the presence or absence of working examples;

The specification provides examples of a 65 and 70 kDa protein comprising the amino acid sequences of SEQ ID No: 3-6. These proteins possessed a pyranose

oxidase activity. The specification provides examples of how the cDNA encoding the above protein was identified.

The specification does not provide examples of what regions, domains or sequences that are required for the protein to maintain the antimicrobial activity. As minor changes in the nucleotide or amino acid sequences may produce profound changes in biological activity (see Lazar *et al.* above), direction should be provided as to what is the minimal sequence necessary for the protein to maintain the antimicrobial activity.

6) the quantity of experimentation necessary;

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate all nucleic acids with 50% identity to SEQ ID NO: 1 encoding proteins with antimicrobial activity. Making all possible substitutions, insertions and deletions in an nucleic acid molecule so that at least 50% sequence identity is maintained to SEQ ID NO: 1 would require making and analyzing an innumerable population of nucleic acids.

It is the specification, not the knowledge of one skill in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. As it is not clear that a gene of at least 50% homology to SEQ ID NO: 1 will encode an antimicrobial protein, a person of ordinary skill in the art would not be able to identify all genes sharing at least 50% homology to SEQ ID NO: 1 and possessing antimicrobial activity without undue experimentation

7) the state of the prior art; and,

Included in the discussion of the predictability or unpredictability of the art (see factor 3).

8) the relative skill of those skilled in the art;

It is concluded that a person skilled in the art would be unable to identify genes encoding antimicrobial proteins given the above discussion. To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. As such, a person skilled in the art is only taught how to identify the cDNA of SEQ ID NO: 1.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

4. Applicant argues at page 10 of Paper #13 that the gene is defied both structurally and functionally by the claims. Applicant also notes that the claims are directed to a novel gene and that the claims are designed to give maximum breadth.

Applicant's arguments are considered but are not convincing. The scope of the claims have extended beyond the subject matter that is enabled by the specification as is argued in this rejection. For instance, one embodiment of claim 11 is a gene with 50% homology to SEQ ID NO: 1. As stated above, homology does not predict the functional activity of the protein and the specification fails to provide guidance what domain or region in predictive of such an activity. Furthermore, claim 12 then expands the breath of the claim to any gene that will bind with low stringency (45 C) to a DNA sequence that shares 50% identity to SEQ ID NO: 1. The structure and function of this entity can not be predicited with any reasonable certainty. Thus, the rejection is maintained.

New Objections and Rejections

Claim Objections

5. Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 12 expands the breath of the claim to any gene that will bind with low stringency (45 C) to a DNA sequence that shares 50% identity to SEQ ID NO: 1. Claim 12 reads upon a gene that has less than 50% homology to SEQ ID NO: 1 and therefore, does not limit the parent claim 11.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 29-31 are directed to a genus of polynucleotides that hybridize under a broad set of hybridization conditions in which the temperature is modified between room temperature, 45 C or 68 C. As recited, the claims do clearly identify a structural element that would define a genus of polynucleotides encoding a protein with a function of pyranose oxidasae activity. Given broad range of hybridization conditions, millions of nucleic acids of unpredicted, non-obvious sequence or structure, would hybridize to SEQ ID NO: 1. Therefore, as the claims describe a large number of structurally unrelated sequences, the claims fail to clearly describe what is in possession by the Applicant, which is a nucleic acid of SEQ ID NO: 1.

8. Claim 24 is drawn to the genus of transgenic organism comprising SEQ ID NO:1, encoding SEQ ID NO: 2. Neither the claim nor the specification discloses the phenotype of the claimed organism. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by

complete structure. It is not realistic to expect that the complete structure of a transgenic animal could be described, therefore the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described. In this case, the specification does not provide a disclosure which enables a skilled artisan to produce any of the animals of the claimed genus. The amount of description required to convey to one of skill in the art that applicant is in possession of the claimed invention is inversely related to the predictability of the art. A skilled artisan cannot currently predict with certainty the phenotype of a hypothetical transgenic animal because of the array of uncontrolled variables which affect transgene expression e.g., integration site, inactivation by methylation, position effects, availability of appropriate transcription factors, etc. The instant specification does not disclose a single working example of any species of the claimed genus of transgenic mice. In view of the unpredictability of transgenic animal phenotypes, this disclosure is insufficient to convey to one of skill in the art that applicant was in possession of the invention at the time of filing.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-20, 22-24, 28, 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite as it is unclear how the polypeptides will be combined. Claims 12-18, 22-24, 28 depend from claim 11 and do not clarify the ambiguity.

Claims 19, 20, and 32 are indefinite as the claims are directed to an oligonucleotide but recite the use of two domain sequences for determination of the sequence. It is unclear how two domains would be used to generate a single sequence.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 19 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Griffais (US 6559294). Claims 19 are 32 are directed to a product-by-process. Griffais teach a primer sequence that is identical to SEQ ID NO: 1 for 15 bp and modified by an additional 5 bp (See sequence 1839). Thus, the reference anticipates the claimed invention.

Applicant is reminded that the final product of the process recited in the claim is taught by Griffais, not the process itself.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (571) 272-0959. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for regular communications to the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
March 18, 2004
SKS

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER